IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Lih-Ling Lin, *et al.*	Group Art Unit: 1646
Serial No.:	Examiner: J. Ulm
Filed: herewith	
For: *Novel TNF Receptor Death Domain Ligand Proteins and Inhibitors of Ligand Binding*	
Attorney Docket No.: GFN-5232CP4DV3CN	

Commissioner for Patents
Arlington, VA 22202

CERTIFICATION UNDER 37 CFR 1.10

Date of Deposit: November 20, 2001 Mailing Label Number: EL 833 313 215 US

I hereby certify that this 37 CFR 1.53(d) request and the documents referred to therein as enclosed are being deposited with the United States Postal Service on the date indicated above in an envelope as "Express Mail Post Office to Addressee" service under 37 CFR 1.10 and addressed to the Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 2327, Arlington, VA 22202.

Ilidio P. Cardoso
Name of Person Mailing Paper

Signature of Person Mailing Paper

PRELIMINARY AMENDMENT

Dear Sir:

Prior to examination, please amend this application as follows:

In the Specification:

Please delete the first paragraph on page 1 and insert the following re-written paragraph:

--This application is a continuation application of U.S. Serial No. 09/185,258, filed on November 2, 1998, pending, which in turn is a divisional application of U.S. Serial No. 08/840,042, filed on April 24, 1997, now abandoned, which is a divisional of U.S. Serial No. 08/839,032, filed on April 23, 1997, issued as U.S. Patent No. 5,891,675,

which is a divisional of U.S. Serial No. 08/698,551, filed on August 15, 1996, issued as U.S. Patent No. 5,712,381, which is a continuation-in-part of U.S. Serial No. 08/602,228, filed on February 15, 1996, issued as U.S. Patent No. 5,843,675, which is a continuation-in-part of U.S. Serial No. 08/533,901, filed September 26, 1995, issued as U.S. Patent No. 5,852,173, which is a continuation-in-part of U.S. Serial No. 08/494,440, filed June 19, 1995, issued as U.S. Patent No. 5,849,501, which is a continuation-in-part of U.S. Serial No. 08/327,514, filed October 19, 1994, now abandoned. The contents of all of the aforementioned applications are hereby incorporated by reference.--

Please amend the paragraph beginning at page 14, line 30 as follows:

--A full-length clone corresponding to clone 1TU was also isolated and identified as "clone 33-1B". The nucleotide sequence of clone 33-1B is reported as SEQ ID NO:17. Nucleotides 14 to 2404 of SEQ ID NO:17 encode a TNF-R1-DD ligand protein, the amino acid sequence of which is reported as SEQ ID NO:18. Amino acids 488 to 797 of SEQ ID NO:18 correspond to amino acids 1 to 310 of SEQ ID NO:10 (clone 1TU). Clone 33-1B was deposited with the American Type Culture Collection on Aug. 13, 1996 and given the accession number ATCC 98137.--

Please amend the paragraph beginning at page 33, line 33 as follows:

--Clone 3TW was isolated from the WI38 cDNA library using clone 3DD as a probe. Clone 3TW was expressed. Fig. 6 is an autoradiograph which demonstrates expression of 3TW (indicated by arrow).--

In the Claims:

Please cancel claims 1-12, 14, 15, 17, 26-46 and amend claims 13, 16, 18, 19, 20, 21, 23, and 24 as follows:

13. (Amended) A composition comprising an antibody which selectively binds to an isolated polypeptide selected from the group consisting of:

a) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:2, or a fragment thereof;

b) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:4, or a fragment thereof;

c) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:6, or a fragment thereof;

d) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:8, or a fragment thereof;

e) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:10, or a fragment thereof;

f) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:12, or a fragment thereof;

g) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:14, or a fragment thereof;

h) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:16, or a fragment thereof; and

i) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:18, or a fragment thereof.

16. (Amended) A method of preventing or ameliorating an inflammatory condition in a subject comprising administering to the subject a therapeutically effective amount of an isolated polypeptide selected from the group consisting of:

a) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:2, or a fragment thereof;

b) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:4, or a fragment thereof;

c) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:6, or a fragment thereof;

d) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:8, or a fragment thereof;

e) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:10, or a fragment thereof;

f) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:12, or a fragment thereof;

g) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:14, or a fragment thereof;

h) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:16, or a fragment thereof; and

i) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:18, or a fragment thereof,

thereby preventing or ameliorating an inflammatory condition.

18. (Amended) A method of inhibiting TNF-R death domain binding in a subject comprising administering to the subject a therapeutically effective amount of an isolated polypeptide selected from the group consisting of:

a) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:2, or a fragment thereof;

b) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:4, or a fragment thereof;

c) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:6, or a fragment thereof;

d) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:8, or a fragment thereof;

e) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:10, or a fragment thereof;

f) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:12, or a fragment thereof;

g) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:14, or a fragment thereof;

h) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:16, or a fragment thereof; and

i) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:18, or a fragment thereof,

thereby inhibiting TNF-R death domain binding in a subject.

19. (Amended) A method of preventing or ameliorating an inflammatory condition in a subject comprising administering to a mammalian subject a

therapeutically effective amount of a composition comprising a pharmaceutically acceptable carrier and a protein selected from the group consisting of IGFBP-5 and fragments thereof having TNF-R1-DD ligand protein activity.

20. (Amended) A method of inhibiting TNF-R death domain binding in a subject comprising administering to a mammalian subject a therapeutically effective amount of a composition comprising a pharmaceutically acceptable carrier and a protein selected from the group consisting of IGFBP-5 and fragments thereof having TNF-R1-DD ligand protein activity.

21. (Amended) A composition comprising an inhibitor of TNF-R death domain binding identified according to the method comprising the steps of:

(a) combining a TNF-R1 death domain protein with a composition comprising a TNF-R1-DD intracellular ligand protein, said combination forming a first binding mixture;

(b) measuring the amount of binding between the TNF-R1 death domain protein and the TNF-R1-DD ligand protein in the first binding mixture;

(c) combining a compound with the TNF-R1 death domain protein and a TNF-R1-DD intracellular ligand protein to form a second binding mixture;

(d) measuring the amount of binding in the second binding mixture; and

(e) comparing the amount of binding in the first binding mixture with the amount of binding in the second binding mixture;

wherein the compound is capable of inhibiting TNF-R1 death domain binding when a decrease in the amount of binding of the second binding mixture occurs.

23. (Amended) A method of preventing or ameliorating an inflammatory condition in a subject comprising administering to a mammalian subject a therapeutically effective amount of the composition of claim 22.

24. (Amended) A method of inhibiting TNF-R death domain binding in a subject comprising administering to a mammalian subject a therapeutically effective amount of the composition of claim 22.

Please add new claims 47-51 have as follows:

47. (New) A method of inhibiting TNF-R death domain binding in a subject comprising administering to the subject a therapeutically effective amount of a composition of claim 13.

48. (New) A method of preventing of ameliorating an inflammatory condition in a subject comprising administering to the subject a therapeutically effective amount of a composition of claim 13.

49. (New) The method of any one of claims 16, 19, and 23, wherein the inflammatory condition is selected from the group consisting of cachexia, autoimmune disease, graft versus host reaction, osteoporosis, colitis, myelogenous leukemia, diabetes, wasting, and atherosclerosis.

50. (New) The method of claim 16, wherein said polypeptide further comprises a pharmaceutically acceptable carrier.

51. (New) The method of claim 18, wherein said polypeptide further comprises a pharmaceutically acceptable carrier.

REMARKS

Claims 1-12, 14, 15, 17, 26-46 have been canceled. Claims 13, 16, 18, 19, 20, 21, 23, and 24 have been amended and new claims 47-51 have been added. Accordingly, claims 13, 16, 18-25, and 47-51 are currently pending.

Support for the amendments to claims 13, 16, 18, 19, 20, 21, 23, and 24 and new claims 47-51 may be found in the specification and claims as originally filed.

Specifically, support for claims 47 and 48 may be found in the specification at, for example, page 23, line 30 through page 24, line 21. Support for claim 49 may be found in the specification at, for example, page 20, lines 7-14.

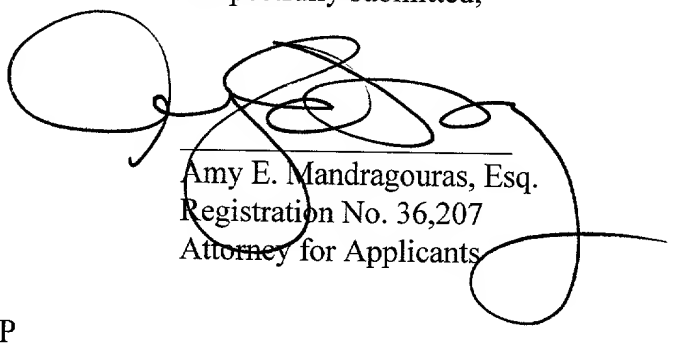
Applicants submit herewith a **"Version with Markings to Show Changes Made,"** which indicates the specific amendments made to the specification and the claims. *No new matter has been added.*

Any amendments to and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite prosecution. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

CONCLUSION

It is respectfully submitted that this application is in condition for allowance. If a telephone conversation with Applicants' attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' attorney at (617) 227-7400.

Respectfully submitted,



Amy E. Mandragouras, Esq.
Registration No. 36,207
Attorney for Applicants

LAHIVE & COCKFIELD, LLP
28 State Street
Boston, MA 02109
Tel. (617) 227-7400

Dated: November 20, 2001

Version with Markings to Show Changes Made

In the specification

The first paragraph on page 1 has been replaced with the following re-written paragraph:

This application is a divisional application of U.S. Serial No. 09/185,258, filed on November 2, 1998, pending, which in turn is a divisional application of U.S. Serial No. 08/840,042, filed on April 24, 1997, now abandoned, which is a divisional of U.S. Serial No. 08/839,032, filed on April 23, 1997, issued as U.S. Patent No. 5,891,675, which is a divisional of U.S. Serial No. 08/698,551, filed on August 15, 1996, issued as U.S. Patent No. 5,712,381, which is a continuation-in-part of U.S. Serial No. 08/602,228, filed on February 15, 1996, issued as U.S. Patent No. 5,843,675, which is a continuation-in-part of U.S. Serial No. 08/533,901, filed September 26, 1995, issued as U.S. Patent No. 5,852,173, which is a continuation-in-part of U.S. Serial No. 08/494,440, filed June 19, 1995, issued as U.S. Patent No. 5,849,501, which is a continuation-in-part of U.S. Serial No. 08/327,514, filed October 19, 1994, now abandoned. The contents of all of the aforementioned applications are hereby incorporated by reference.

The paragraph beginning at page 14, line 30 has been amended as follows:

A full-length clone corresponding to clone 1TU was also isolated and identified as "clone 33-1B". The nucleotide sequence of clone 33-1B is reported as SEQ ID NO:17. Nucleotides 14 to 2404 of SEQ ID NO:17 encode a TNF-R1-DD ligand protein, the amino acid sequence of which is reported as SEQ ID NO:18. Amino acids 488 to 797 of SEQ ID NO:18 correspond to amino acids 1 to 310 of SEQ ID NO:10 (clone 1TU). Clone 33-1B was deposited with the American Type Culture Collection on Aug. 13, 1996 and given the accession number ATCC 98137.

The paragraph beginning at page 33, line 33, has been amended as follows:

Clone 3TW was isolated from the WI38 cDNA library using clone 3DD as a ~~porbe~~ probe. Clone 3TW was expressed. Fig. 6 is an autoradiograph which demonstrates expression of 3TW (indicated by arrow).

In the Claims:

Claims 1-12, 14, 15, 17, 26-46 have been cancelled.

Claims 13, 16, 18, 19, 20, 21, 23, and 24 have been amended as follows:

13. (Amended) A composition comprising an antibody which ~~specifically reacts with the TNF-R1-DD ligand protein of claim 8~~ selectively binds to an isolated polypeptide selected from the group consisting of:

a) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:2, or a fragment thereof;

b) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:4, or a fragment thereof;

c) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:6, or a fragment thereof;

d) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:8, or a fragment thereof;

e) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:10, or a fragment thereof;

f) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:12, or a fragment thereof;

g) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:14, or a fragment thereof;

h) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:16, or a fragment thereof; and

i) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:18, or a fragment thereof.

16. (Amended) A method of preventing or ameliorating an inflammatory condition ~~which comprises~~ in a subject comprising administering to the subject a therapeutically effective amount of ~~a composition of claim 12~~ an isolated polypeptide selected from the group consisting of:

a) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:2, or a fragment thereof;

b) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:4, or a fragment thereof;

c) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:6, or a fragment thereof;

d) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:8, or a fragment thereof;

e) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:10, or a fragment thereof;

f) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:12, or a fragment thereof;

g) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:14, or a fragment thereof;

h) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:16, or a fragment thereof; and

i) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:18, or a fragment thereof,

thereby preventing or ameliorating an inflammatory condition.

18. (Amended) A method of inhibiting TNF-R death domain binding in a subject comprising administering to the subject a therapeutically effective amount of ~~a composition of claim 12~~ an isolated polypeptide selected from the group consisting of:

a) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:2, or a fragment thereof;

b) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:4, or a fragment thereof;

c) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:6, or a fragment thereof;

d) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:8, or a fragment thereof;

e) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:10, or a fragment thereof;

f) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:12, or a fragment thereof;

g) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:14, or a fragment thereof;

h) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:16, or a fragment thereof; and

i) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:18, or a fragment thereof,

thereby inhibiting TNF-R death domain binding in a subject.

19. (Amended) A method of preventing or ameliorating an inflammatory condition ~~which comprises~~ in a subject comprising administering to a mammalian subject a therapeutically effective amount of a composition comprising a pharmaceutically acceptable carrier and a protein selected from the group consisting of IGFBP-5 and fragments thereof having TNF-R1-DD ligand protein activity.

20. (Amended) A method of inhibiting TNF-R death domain binding in a subject comprising administering to a mammalian subject a therapeutically effective amount of a composition comprising a pharmaceutically acceptable carrier and a protein selected from the group consisting of IGFBP-5 and fragments thereof having TNF-R1-DD ligand protein activity.

21. (Amended) A composition comprising an inhibitor of TNF-R death domain binding identified according to the method ~~of claim 14~~ comprising the steps of:

(a) combining a TNF-R1 death domain protein with a composition comprising a TNF-R1-DD intracellular ligand protein, said combination forming a first binding mixture;

(b) measuring the amount of binding between the TNF-R1 death domain protein and the TNF-R1-DD ligand protein in the first binding mixture;

(c) combining a compound with the TNF-R1 death domain protein and a TNF-R1-DD intracellular ligand protein to form a second binding mixture;

(d) measuring the amount of binding in the second binding mixture; and

(e) comparing the amount of binding in the first binding mixture with the amount of binding in the second binding mixture;

wherein the compound is capable of inhibiting TNF-R1 death domain binding when a decrease in the amount of binding of the second binding mixture occurs.

23. (Amended) A method of preventing or ameliorating an inflammatory condition in a subject comprising administering to a mammalian subject a therapeutically effective amount of the composition of claim 22.

24. (Amended) A method of inhibiting TNF-R death domain binding in a subject comprising administering to a mammalian subject a therapeutically effective amount of the composition of claim 22.

New claims 47-51 have been added as follows:

47. (New) A method of inhibiting TNF-R death domain binding in a subject comprising administering to the subject a therapeutically effective amount of a composition of claim 13.

48. (New) A method of preventing of ameliorating an inflammatory condition in a subject comprising administering to the subject a therapeutically effective amount of a composition of claim 13.

49. (New) The method of any one of claims 16, 19, and 23, wherein the inflammatory condition is selected from the group consisting of cachexia, autoimmune disease, graft versus host reaction, osteoporosis, colitis, myelogenous leukemia, diabetes, wasting, and atherosclerosis.

50. (New) The method of claim 16, wherein said polypeptide further comprises a pharmaceutically acceptable carrier.

51. (New) The method of claim 18, wherein said polypeptide further comprises a pharmaceutically acceptable carrier.

Appendix A

13. A composition comprising an antibody which selectively binds to an isolated polypeptide selected from the group consisting of:

a) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:2, or a fragment thereof;

b) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:4, or a fragment thereof;

c) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:6, or a fragment thereof;

d) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:8, or a fragment thereof;

e) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:10, or a fragment thereof;

f) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:12, or a fragment thereof;

g) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:14, or a fragment thereof;

h) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:16, or a fragment thereof; and

i) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:18, or a fragment thereof.

16. A method of preventing or ameliorating an inflammatory condition in a subject comprising administering to the subject a therapeutically effective amount of an isolated polypeptide selected from the group consisting of:

a) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:2, or a fragment thereof;

b) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:4, or a fragment thereof;

c) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:6, or a fragment thereof;

d) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:8, or a fragment thereof;

e) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:10, or a fragment thereof;

f) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:12, or a fragment thereof;

g) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:14, or a fragment thereof;

h) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:16, or a fragment thereof; and

i) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:18, or a fragment thereof,

thereby preventing or ameliorating an inflammatory condition.

18. A method of inhibiting TNF-R death domain binding in a subject comprising administering to the subject a therapeutically effective amount of an isolated polypeptide selected from the group consisting of:

a) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:2, or a fragment thereof;

b) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:4, or a fragment thereof;

c) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:6, or a fragment thereof;

d) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:8, or a fragment thereof;

e) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:10, or a fragment thereof;

f) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:12, or a fragment thereof;

g) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:14, or a fragment thereof;

h) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:16, or a fragment thereof; and

i) a polypeptide encoding a TNF-RI-DD ligand protein comprising the amino acid sequence of SEQ ID NO:18, or a fragment thereof,
thereby inhibiting TNF-R death domain binding in a subject.

19. A method of preventing or ameliorating an inflammatory condition in a subject comprising administering to a mammalian subject a therapeutically effective amount of a composition comprising a pharmaceutically acceptable carrier and a protein selected from the group consisting of IGFBP-5 and fragments thereof having TNF-R1-DD ligand protein activity.

20. A method of inhibiting TNF-R death domain binding in a subject comprising administering to a mammalian subject a therapeutically effective amount of a composition comprising a pharmaceutically acceptable carrier and a protein selected from the group consisting of IGFBP-5 and fragments thereof having TNF-R1-DD ligand protein activity.

21. A composition comprising an inhibitor of TNF-R death domain binding identified according to the method comprising the steps of:

(a) combining a TNF-R1 death domain protein with a composition comprising a TNF-R1-DD intracellular ligand protein, said combination forming a first binding mixture;

(b) measuring the amount of binding between the TNF-R1 death domain protein and the TNF-R1-DD ligand protein in the first binding mixture;

(c) combining a compound with the TNF-R1 death domain protein and a TNF-R1-DD intracellular ligand protein to form a second binding mixture;

(d) measuring the amount of binding in the second binding mixture; and

(e) comparing the amount of binding in the first binding mixture with the amount of binding in the second binding mixture;

wherein the compound is capable of inhibiting TNF-R1 death domain binding when a decrease in the amount of binding of the second binding mixture occurs.

22. The composition of claim 21 further comprising a pharmaceutically acceptable carrier.

23. A method of preventing or ameliorating an inflammatory condition in a subject comprising administering to a mammalian subject a therapeutically effective amount of the composition of claim 22.

24. A method of inhibiting TNF-R death domain binding in a subject comprising administering to a mammalian subject a therapeutically effective amount of the composition of claim 22.

25. A composition comprising a pharmaceutically acceptable carrier and a protein selected from the group consisting of IGFBP-5 and fragments thereof having TNF-R1-DD ligand activity.

47. (New) A method of inhibiting TNF-R death domain binding in a subject comprising administering to the subject a therapeutically effective amount of a composition of claim 13.

48. (New) A method of preventing of ameliorating an inflammatory condition comprising administering to the subject a therapeutically effective amount of a composition of claim 13.

49. (New) The method of any one of claims 16, 19, and 23, wherein the inflammatory condition is selected from the group consisting of cachexia, autoimmune disease, graft versus host reaction, osteoporosis, colitis, myelogenous leukemia, diabetes, wasting, and atherosclerosis.

50. (New) The method of claim 16, wherein said polypeptide further comprises a pharmaceutically acceptable carrier.

51. (New) The method of claim 18, wherein said polypeptide further comprises a pharmaceutically acceptable carrier.